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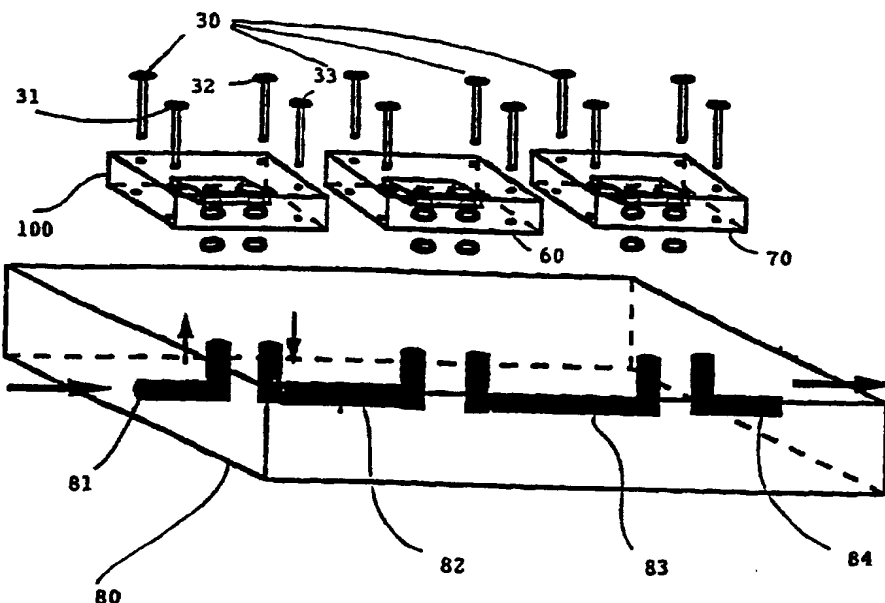
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(54) Title: INTEGRATED CHEMICAL SYNTHESIZERS



(57) Abstract

A modular reactor system (see figure) and method for synthesizing chemical compounds characterized by a uniform temperature throughout the reaction mixture by use of a continuous flow reactor (100, 60, 70) under high pressure. The apparatus includes a number of generic components such as pumps, flow channels (81, 82, 83, 84), manifolds, flow restrictors, and valves. Modular reactors (100, 60, 70), separator and analyzers on an assembly board (80) provide a system where a modular reactor unit (100, 60, 70) has an internal diameter of up to 100 micrometers to optimize control of residence time within a reaction zone.

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INTEGRATED CHEMICAL SYNTHESIZERS

FIELD OF THE INVENTION

This invention relates to an improved method and apparatus for continuously synthesizing chemical compounds under controlled and regulated reaction conditions. More particularly, this invention relates to a modular multi-component system with interchangeable microreactors, that can be used in tandem, series, or individually. Flow and reaction conditions of the modular multi-component system can be monitored to regulate the reaction process and/or create an optimal environment for the synthesis of the desired chemical compounds.

BACKGROUND OF THE INVENTION

Complex inorganic and organic compounds, e.g., drugs, monomers, organometallic compounds, semiconductors, polymers, peptides, oligonucleotides, polynucleotides, carbohydrates, amino acids, and nucleic acids belong to a class of materials having significant diagnostic, medicinal and commercial importance. Many techniques have been developed to produce these materials. However, the systems necessary to carry-out and prepare or synthesize these complex materials are inefficient, wasteful and often times require reagent quantities far in excess of what is available. This is especially the case in those instances where microliter quantities are involved. The use of conventional substrates requires larger sized systems with the incumbent process control problems. Additionally, reagent or reactant stability must be considered and accurately controlled to render the process efficient in yield and cost.

The production of these complex materials requires a versatile system that can handle different reaction and separatory schemes. Most synthesizers provide only for a single type of

reactor, e.g., electrochemical, catalytic, solid phase support, enzymatic, photochemical, or hollow chamber.

For example, U.S. Patent No. 4, 517,338 to
5 Urdea teaches a system for sequencing amino acids that uses one or more elongated tubular reaction zones. The reactors for each reaction zone are similar in structure with an internal diameter (I.D.) of a 0.1 to 1.0 cm. Each of the reactors
10 needs a glass frit to support the solid-phase material.

U.S. Patent No. 4,960,566 to Mochida relates to an automatic analyzer for conveying reagent coated capillary tubes along process lines where
15 reagents are added, reacted and analyzed. The Mochida patent indicates at Column 3 that the inner diameter of the capillary tubes appears to be no smaller than 0.95 mm. The process of Mochida provides for serial processing of reaction
20 tubes of a common design. Independent temperature control of parallel tubes and modularity are not provided.

U.S. Patent No. 4,276,048 to Leaback teaches capillary size reaction containers for volumetric
25 transfer of fluids to a microtitre tray. The system is essentially batch-like and does not

involve continuous flow or automatic valving to selectively direct the flow of a particular reagent to one reaction column as opposed to another to provide for amino acid sequencing within the tube.

U.S. Patent No. 5,176,881 to Sepaniak et al. teaches a fiber optic-based regenerable biosensor that uses a capillary feed mechanism.

U.S. Patent No. 4,362,699 to Verlander et al. relates to high pressure peptide synthesizers and uses a plurality of reservoirs that communicate via a switching valve to a reactor 90. The Verlander system was designed to overcome the limitations of the Merrifield system which apparently had a limitation of synthesizing peptides having no more than 10 amino acids. The system can also include a mixer upstream of the reactor to mix the protected amino acid solution and the appropriate activating reagent. Column 6 lines 3-12. The system is automated and the reactor column contains a polystyrene resin which is derivatized with a protected amino acid.

U.S. Patent No. 4,458,066 to Caruthers et al. teaches an amino acid synthesizer and uses a plurality of reagent reservoirs connected via a manifold to a tubular reactor. The reactor

column 10 includes a solid silica gel matrix derivatized for the sequencing operation and, via a valve can be communicated to a UV detector 58. The reactor is taught to be sized for a 1 ml. volume.

U.S. Patent No. 4,728,502 Hamill relates to an amino acid sequencer that utilizes a plurality of stacked disks each having a plurality of chambers and resulting in a plurality of parallel columns. Although the contents of each chamber of each disk are removable, the respective columns formed by a series of chambers in the stacked disk are not.

U.S. Patent No. 4,961,915 to Martin relates to a DNA sequencing system. A rotatable turntable conveys fluids along narrow channels that are open on an upper end. This allows individual dispensing of additional reagents along the length of the channel. The Martin patent does not provide a continuous flow valved reaction system or direct in-line valving to control reagents directly to one or more channels. In addition, the grooves or channels are in a common base and replacement or scale up is not possible.

The object of the subject invention is to provide an Integrated Chemical Synthesizer (ICS)

system that is modular in design and provides for continuous flow operation. The modular nature of the ICS system allows for the use of one or more of the same type of reactor, or a variety of different types of reactors, each having microliter capacity. The reactors of the ICS system are capable of being used individually, together, and interchangeably with one another and can be of the thermal, electrochemical, catalytic, enzymatic, photochemical, or hollow chamber type. The modular nature of the system, component parts, e.g., the reactors, flow channels, sensors, detectors, temperature control units, allows easy replacement and/or interchangeability of the component parts and provides a versatility not offered by existing systems.

The ICS system provides for uniform temperature control for continuous flow reactors under elevated pressures. This allows for precise control of residence time within a reaction zone. ICS synthesizers would thus exhibit a number of advantages when compared to conventional systems of larger size. Heat transfer, which depends upon the ratio of surface area (A) to volume (V), would be much better for the smaller reactors. This is a major advantage, for example, in capillary zone

electrophoresis compared to large scale gel electrophoresis. This configuration also allows faster heat dissipation and faster thermal control.

5 The ICS system would not only present better control of reaction conditions, but it would allow for quenching reactions at certain stages to prevent further reaction. The ICS system would also, due to its modular nature, provide for
10 serial placement of reactors to allow controlled sequential reactions of intermediates. Moreover, it should be much easier to scale-up reactions based on the ICS approach because one would simply add additional modules of exactly the same type to
15 increase output. For industrial synthesis, the ICS approach would eliminate proceeding from a bench scale reactor through a variety of different pilot plant configuration to a full-sized reactor.

 Moreover, the inherent redundancy of multiple
20 parallel ICS reactors implies fewer operational problems with the failure of a few reactors, especially if the system is set up for easy replacement and repair of a single ICS line. As a result, such systems are probably inherently
25 much safer. The rupture of a single ICS reactor, even at high temperature and pressure, would cause

negligible damage since the total volume and amounts of reactants released would be small. This would be especially beneficial when carrying out reactions under extreme conditions, e.g., the
5 high temperatures and pressure in supercritical water and other fluids. Overall the ICS system should result in better yields of products with less waste and disposal problems because of better control of reaction variables.

10 As a result of the ICS modular system, the problems of inefficiency, lack of versatility, down-time, reagent/reactant waste and excessive cost have been overcome.

SUMMARY OF THE INVENTION

15 Accordingly, the present invention provides a novel system for synthesizing chemical compounds. The system of the present invention can also synthesize compounds under a variety of process conditions, e.g., uniform temperature in
20 a continuous flow reactor under high pressure, non-uniform temperatures and high pressure.

In accordance with one aspect of the present invention a modular multicomponent system is provided. The system, e.g. a kit, provides a
25 reaction system capable of handling a variety of

reactions by using a reactor unit having a reaction chamber with an I.D. of from about 1 μm up to about 1mm, and more preferably 1-100 μm . Specifically, a modular "chip" type reactor unit
5 is formed by applying a photoresist layer onto an upper surface of a SiO_2 or Si substrate and forming a reactor design thereon. The reactor design is developed and etched with acid to form a reactor chamber having an ID less than 100 μm . The
10 chamber is covered and the unit mounted on an assembly board containing fluid conveying channels, with fastening means, to provide for flow to and from the reactor chamber.

In accordance with another aspect of the
15 present invention, a modular multicomponent system containing a plurality of interchangeable reaction vessels, alike or different, in parallel or series, and capable of handling reactions volumes from about 1nL up to about 10 μL , and more
20 preferably 1nL-10 μL is provided.

In still another aspect of the present invention, both organic and inorganic compounds can be synthesized.

In yet another aspect of the present
25 invention, a novel system capable of regulating extreme conditions (e.g., supercritical

temperatures and pressures) is provided. This system for synthesizing compounds provides a means for avoiding potential explosions and provides a reliable method for heat dissipation.

5 **BRIEF DESCRIPTION OF THE DRAWINGS**

Figs. 1a-1d show a fabricated chip type reactor unit for the ICS modular system.

10 **Figs. 2** illustrates an exploded view of a chip type reactor unit and the fluid delivery flow channels of an assembly board according to the present invention.

15 **Fig. 3** is an exploded view of one embodiment of the ICS system.

20 **Fig. 4** shows an exemplary ICS system with fluid control and computer interfacing according to the subject invention.

Fig. 5 is a flow chart for preparing t-BuCl using the subject invention.

5 Fig. 6 shows a flow chart for photochemical conversion of dibenzylketone using the ICS system of the subject invention.

10 Fig. 7 is a flow chart illustrating electrochemical reduction of benzoquinone according to the present invention.

15 Fig. 8 is a flow chart for multiphase membrane reactor conversion of benzylpenicillin to 6 amino penicillanic acid (6-APA) using the ICS system.

20 Fig. 9 is a flow chart for converting n-C₇H₁₆ to toluene using the subject invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is broadly directed toward a total modular system that can use a plurality of replaceable and interchangeable cylindrical or rectangular reactors in combination with a mass-based sensor. Generally, the ICS system can include (1) fluid flow handling and control components; (2) mixers; (3) reaction "chip type" units; (3) separatory devices; (4) process variable detectors and controllers; and (5) a computer interface for communicating with a master control center.

The ICS system may also include a support structure for detachably retaining the various components of the system. The support structure can be of the "assembly board type" that will contain pre-arranged flow channels and connector ports. The desired components of the system can be fastened into these connectors by pins. The flow control components that make-up the ICS system can include pumps, flow channels, manifolds, flow restrictors, valves, etc. These components will have the necessary fittings that allow them to be sealed with the pre-arranged or selectively located flow channels or connectors. The flow system can also include detachable mixing

devices, e.g., static or ultrasonic, some of which
can be "chip like" in design. The reaction units,
whether "chip like" or not, can be of the thermal,
electrochemical, photochemical, pressure type and
5 be rectangular or cylindrical in shape.

The separatory components can provide for
membrane separation, concurrent or countercurrent
flow extraction, chromatographic separation,
electrophoretic separation, or distillation. The
10 detectors can include electrochemical,
spectroscopic or fluorescence based detectors to
monitor the reactants, intermediates, or final
products.

The ICS system can include a plurality of
15 individual, detachable reaction units. With a
plurality of units, one of the reaction units may
be structurally different and capable of
permitting a different chemical process of being
performed. For example there may be thermal and
20 photochemical units or electrochemical, thermal
and pressure units. The ICS system can also
include a detachable separation chamber, and an
analyzer capable of monitoring and/or controlling
a process variable. More specifically, a typical
25 embodiment utilizes flow channels, a flow mixer,
at least one electrochemical reaction chamber, an

electrophoretic separation chamber, and an electrochemical analyzer.

In accordance with the preferred embodiment of the present invention, an apparatus for achieving the synthesis described above is illustrated in Fig. 1-9.

The basic concept of the subject invention is to produce a modular system, with components (reactors, separation chambers, analyzers, etc.) that are inexpensive and easily assembled. The subject invention can be assembled on a flow channel assembly board in the same way integrated circuitry chips and other electrical components are assembled on a circuit board. In the ICS system various reactors, analyzer(s), e.g., "chip units," are put together on an "assembly board". Two approaches to assembling such systems would be (a) custom design chips and assembly boards or, (b) the current capillary high pressure liquid chromatography (HPLC)-capillary zone electrophoresis (CZE) approach with microbore tubing (silica, stainless steel) and various connectors, injectors, pumps, etc. In case (a) the chips could be made from silica (SiO_2) (glass), silicon (Si) (as integrated circuit chips),

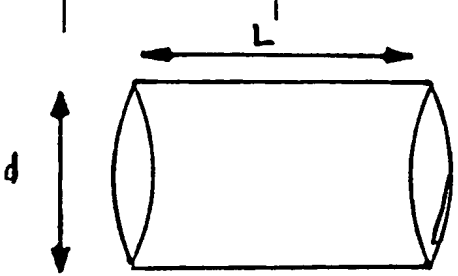
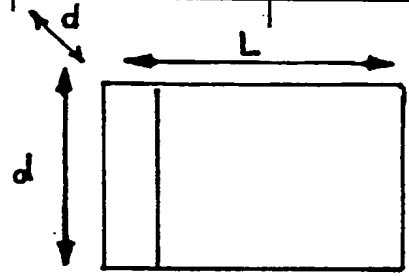
polymers (plastic), and/or metal (stainless steel, titanium).

An example of fabricating a chip unit 100 according to the invention is shown in Figs. 1a-1d. With reference to Figs. 1a-1d, a substrate of SiO_2 or Si is designed to include a rectangular reaction chamber 4. The chamber 4 is formed by photolithographic processes such as those currently used for integrated circuits and circuit boards. A photoresist layer 2 is deposited on the upper surface 6 of the SiO_2 or Si block substrate 1 and, the desired pattern 3 is formed in layer 2 by exposure to the proper image and development techniques. The rectangular reactor chamber 4 is formed by etching the preformed pattern into the substrate, e.g., with HF for SiO_2 to the extent necessary to form a chamber having the desired volume. For complex structures, multiple photolithographic processes may be necessary. Flow channels for the reactor are similarly fabricated using photolithography from the other side of the substrate. A second photoresist layer 7 is placed on lower surface 6, exposed to form port openings 8 and 9. Thereafter, channels 10 and 11 are formed to provide flow communication to reactor chamber 4. Finally, a cover 12 is

attached to close the upper surface 5 to form a top of the reactor 4 and produce the finished chip. Photoresist layers 2 and 7 also include a plurality of patterns 13-16 and 17-20 formed thereon so that through channels for fastening pins can be formed. The reactor could also be fabricated at one time, alternatively, with plastic materials, by injection molding or casting techniques. Micromachining (e.g., using the scanning tunneling microscope or scanning electrochemical microscope) of metals and semiconductor substrates could also be used to make the modular units of the subject invention.

Table 1 shows volume parameters for various ICS reactors.

VOLUMES ICS REACTORS

Calculation of ICS Reactor Volumes					
Cylindrical reactor, $V = \pi d^2 L/4$			Rectangular reactor, $V = d^2 L$		
d (μm)	L (μm)	V (μL)	d (μm)	L (μm)	V (μL)
1	10	7.85E-09	1	10	1.00E-08
1	100	7.85E-08	1	100	1.00E-07
1	1000	7.85E-07	1	1000	1.00E-06
1	1.00E+04	7.85E-06	1	1.00E+04	1.00E-05
10	10	7.85E-07	10	10	1.00E-06
10	100	7.85E-06	10	100	1.00E-05
10	1000	7.85E-05	10	1000	1.00E-04
10	1.00E+04	7.85E-04	10	1.00E+04	1.00E-03
100	10	7.85E-05	100	10	1.00E-04
100	100	7.85E-04	100	100	1.00E-3
100	1000	7.85E-03	100	1000	1.00E-2
100	1.00E+04	7.85E-02	100	1.00E+04	1.00E-1
1000	10	7.85E-03	1000	10	1.00E-2
1000	100	7.85E-02	1000	100	1.00E-1
1000	1000	7.85E-01	1000	1000	1.00E+00
1000	1.00E+04	7.85E+00	1000	1.00E+04	1.00E+01
1 $\mu\text{m} = (1\text{e-}4) \text{ cm}$		1000 $\mu\text{m} = 1 \text{ mm}$			
1 $\mu\text{m}^3 (1\text{e-}9) \mu\text{L}$		1E4 $\mu\text{m} = 1 \text{ cm}$			
					
1 nL = (1e=3) μL					
1 pL = (1e=6) μL					
1 aL = (1e=9) μL					

The different kinds of chip units produced according to the subject invention could then be connected to the assembly board containing the
5 desired flow connections (Fig. 2) and also (not shown) electrical connections to electrodes, heaters, etc. Fig. 2 uses O-rings 40 and 41 (Teflon, Viton) to connect the chip channels 10 and 11 to the corresponding channels 50 and 51 on
10 assembly board 20 and pins 30-37 (or clips) to hold the chip to board 20.

Fig. 3 shows an assembly of several different chips on a single board with interconnections. In Fig. 3 units 100, 60, and 70 are respectively a
15 reactor, a separator and an analyzer. The housings for separator 60 and analyzer 70 are formed in a manner similar to that of reactor unit 100 described above, but include the requisite, structures and components to perform the
20 designated process, e.g., separation, analysis.

In Fig. 3, pins 30-33 connect the units 100, 60 and 70 to assembly board 80 containing channels 81-84 therein. Channels 81 and 82 respectively communicate with channels 10 and 11 in reactor
25 unit 100. Similarly, channels 82 and 83 communicate with the corresponding channels in

unit 60 and channels 83 and 84 communicate with the channels in unit 70.

Alternatively capillary tubing for reactors, detectors, etc., following current HPLC-CZE
5 practice, sized in accordance with the subject disclosure may be assembled on a support board in a similar manner (not shown).

For capillary tubing, connectors, pumps, etc., using the capillary HPLC approach can be
10 obtained from manufacturers, such as, Valco, Swagelok, and Waters. Specialized materials useful in the subject invention reactors and separators can be made from Naflon (ion-exchange) hollow fibers and are manufactured by DuPont.

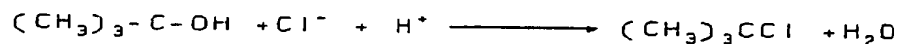
15 If a glass substrate is used for the "chip" units, the walls are already SiO_2 . If a Si substrate is used, SiO_2 can be formed by oxidation in air under controlled temperature conditions. For metal substrates, e.g., Ti, a protective and
20 insulating film (TiO_2) can also be formed by air or anodic oxidation. It is also possible to coat the walls of the tube with catalyst particles, organic films for separations, etc.

Fig. 4 includes an assembly board
25 schematically showing the "chip" type processing units of the subject invention. The assembly board includes a reactor R formed in a manner

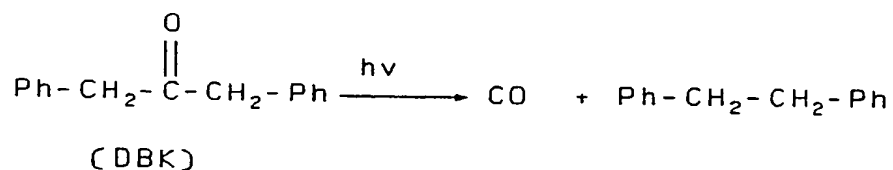
similar to unit 100 above, but includes a heat transfer system. The reactor R communicates with a chip type mixer M_x at the upstream end and a chip type detector D_1 , e.g., unit 100, at the downstream
5 end. The detector D_1 communicates with a chip type separator, e.g., unit 60, which in turn is in fluid communication with a second chip type detector unit D_2 , e.g., unit 70.

The system of Fig. 4 operates as follows:
10 reagents A and B via pressure actuated pumps P_A and P_B , and valves V_A and V_B sequentially or simultaneously flow to the mixer M_x . If isolation of a reagent is necessary, after reagent A is fed to mixer M_x and discharged to the reactor R_1 , a
15 wash fluid W is conveyed via pump P_w and valve V_w to the mixer M_x and discharged. Signals from detectors D_1 , D_2 , thermocouple TC, and flowmeter FM are transmitted to the computer through interface
90 to control the flow of reagents A and B and
20 temperature, or any additional reagents according to the process to be performed by the subject invention.

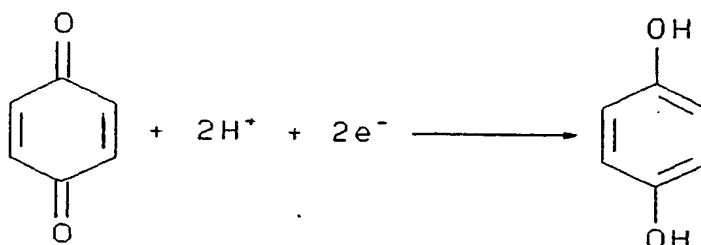
Having now generally described this invention, the following examples are included for
25 purposes of illustration and are not intended as any form of limitation.

Example 1Thermal conversion of t-butanol to t-butyl chloride

With reference to Fig. 5, solutions of
5 concentrated hydrochloric acid 201 and t-butanol
202 are metered through pumps 203, 206 and valves
204, 207 to a mixer 205 to the reaction chamber
208. Temperature in the reaction chamber 208 is
controlled via a heating/cooling system 215 on the
10 assembly board, e.g., 80, to maintain the reaction
temperature (measured by a thermocouple) at about
30-40°C. The two phases that form are separated
in the separator chamber 209 and further
purification of t-BuCl can be accomplished, if
15 desired, by distillation at 50°C in chamber 213
with product being withdrawn via line 214. HCl
and H₂O are withdrawn via line 210 and waste is
discharged via line 212.

Example 2Photochemical conversion of dibenzylketone

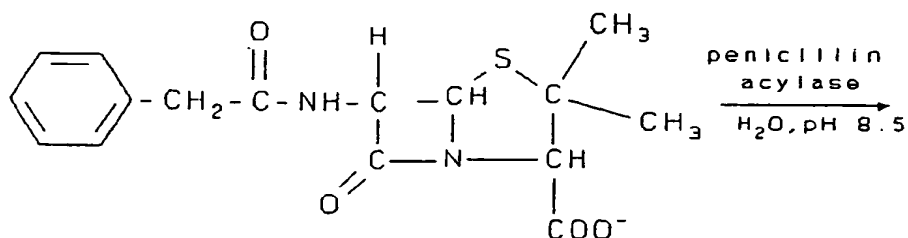
With reference to Fig. 6, dibenzylketone in benzene 301 (0.01 M) is metered via 302 and 303 into the photochemical reaction chamber 304 with at least one transparent wall, where it is irradiated with light 307 from a 450 watt xenon lamp 305 via filter 306. The CO produced 310, in the reaction 309 is vented and the bibenzyl product is purified, if desired, through a chromatographic separator 308 and withdrawn through line 309.

Example 3Electrochemical reduction of benzoquinone

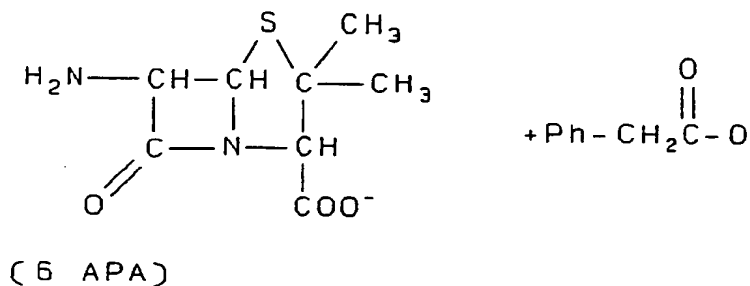
In Fig. 7, an acidic aqueous solution of benzoquinone (0.1 M) 401 is metered (402, 403) into the cathodic chamber 416 of the electrochemical reactor 415. This chamber, e.g. outside a Naflon hollow fiber tube containing the Pt anode and the analyte, contains a carbon or zinc cathode. Anode 408a and cathode 408b are connected to a power supply 407. The current density and flow rate are controlled to maximize current efficiency as determined by analysis of hydroquinone by the electrochemical detector 417. Hydroquinone 410 is extracted in extractor 409 from the resulting product stream with ether 414 metered (412 and 413) from ether supply 411. Alternatively, flow in chamber 415 can be directed to the inner anode chamber with the appropriate controls.

Example 4

Multiphase membrane reactor conversion
of benzylpenicillin (BP) to
6-aminopenicillanic acid (6-APA)



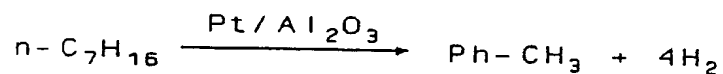
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In Fig. 8, the effluent 501 from a penicillin fermentation reactor containing BP is fed through a filter bank 502 and 503. An aqueous acid 505 is mixed with the filtered BP in mixer 506 and fed to
5 membrane reactor 507. The membrane reactor 507 is, preferably a hollow fiber tube 511 on which the enzyme penicillin acylase has been immobilized. The tube also selectively extracts 6-APA (see J.L. Lopez, S.L. Matson, T.J. Stanley, and J.A. Quinn,
10 in "Extractive Bioconversions," Bioprocess Technologies Series, Vol 2, B. Masttgiasson and O. Holst. Eds., Marcel Dekker, N.Y., 1987). The BP is converted on the wall of the fiber and the product passes into the sweep stream inside the
15 fiber where it can be purified by ion exchange 508. The BP stream 510 is recycled back through the reactor.

Example 5

20 Catalytic conversion (reforming) of n-heptane to toluene



In Fig. 9, liquid n-heptane 601 is metered via 602, 603 into the vaporizing chamber 604 held at 150°C. Toluene in the gas phase is conveyed to

the catalytic reactor 605 containing a packed bed of Pt-Al₂O₃ catalyst held at 400°C. Hydrogen is removed through line 606. The heptane-toluene mixture from reactor 605 is fed to separator 608
5 with toluene being removed through line 609 and heptane through line 607.

Although the invention has been described in conjunction with the specific embodiments, it is evident that many alternatives and variations will
10 be apparent to those skilled in the art in light of the foregoing description. Accordingly, the invention is intended to embrace all of the alternatives and variations that fall within the spirit and scope of the appended claims. Further,
15 the subject matter of the above cited United States Patents are incorporated herein by reference.

WE CLAIM:

1. A modular chemical reaction system comprising:
 - (a) a modular reactor having a reaction chamber volume from about 1nL to about 10 μ L;
 - (b) a separation chamber;
 - (c) an analyzer; and
 - (d) an assembly board for mounting elements (a) - (c) and provide flow communication therebetween.
2. A modular chemical reaction system as recited in claim 1, wherein said reaction chamber is selected from the group consisting of thermal, electrochemical, photochemical, and pressurized reaction chambers.
3. A modular chemical reaction system according to claim 1, wherein said separation chamber is selected from the group consisting of extraction, chromatographic, electrophoretic, membrane, and distillation separation chambers.
4. A modular chemical reaction system according to claim 1, wherein said analyzer is selected from the group consisting of electrochemical, spectroscopic, and fluorescence analyzers.

5. A modular chemical reaction system according to claim 1, which further includes interchangeable modular units.

6. A modular chemical reaction kit comprising:

- 5 (a) a support structure for detachably retaining a plurality of physical and/or chemical process units;
- 10 (b) a plurality of individual detachable physical and/or chemical process units, at least one of said units being a reaction unit and another of said process units being structurally different and capable of permitting a
- 15 different process to be performed;
- (c) a plurality of detachable and interchangeable flow channels;
- (d) at least one detachable separation chamber;
- 20 (e) at least one analyzer capable of monitoring and/controlling a process variable; and
- (f) a computer interface for communicating a signal from (e) to
- 25 a control system.

7. The kit according to Claim 6, wherein there are at least three reaction units, two of which are identical.
8. The kit according to Claim 6, wherein said
5 flow channel and walls of said reaction unit are coated with SiO_2 .
9. The kit according to Claim 8, wherein said reaction unit has an I.D of about $1\mu\text{m}$ to about $100\mu\text{m}$.
10. A reaction chamber having a through flow
10 channel, said flow channel having an I.D. of between about $1\mu\text{m}$ to about $100\mu\text{m}$ and length of about 1 cm.
11. The reaction chamber according to Claim 10,
15 wherein the said reaction chamber has a wall formed from a material selected from glass, metal, or synthetic polymeric material and is coated on the inside thereof with silicon dioxide
12. A method for synthesizing chemical compounds
20 comprising the steps of:

- (a) mixing reactants and feeding the reactants to a modular reactor having an ID no greater than 100 μm ;
- 5 (b) controlling the reaction time or temperature of said reactants in said modular reaction chamber;
- (c) separating a reaction product from the by-products; and
- 10 (d) analyzing said products.

13. A method according to claim 12 wherein said reaction temperature is from about 30 to about 150°C.

14. A method of making a modular reactor having
15 an ID less than 100 μm comprising,

- a) forming a rectangular reaction chamber by,
 - 1) applying a photoresist layer onto an upper surface of a SiO_2 or Si substrate;
 - 20 2) developing a reactor design pattern on said layer;
 - 3) acid etching the exposed pattern to form a reactor chamber having
25 an ID less than 100 μm ;

- 5
- 4) covering an upper surface of the substrate with a cover to close the open upper surface of the reactor chamber to form a reactor unit; and
- 5) repeating the applying, developing and etching steps above to form fluid conduits and fastening channels in said substrate; and
- 10 b) mounting the reactor unit on an assembly board containing fluid conveying channels with fastening means to provide for flow to and from the reactor unit.
- 15 15. A modular reactor comprising,
- 1) a block substrate containing a chamber defining a volume of from about 1nL up to about 10 μ L in volume;
- 2) flow channels formed within the block substrate for flow of reactants to and products from said reaction chamber;
- 20 3) fastening means to permit said modular reactor to be connected to an assembly board.

16. A modular reactor according to claim 15, wherein said chamber volume is between about 1nL-1.01 μ L in volume.

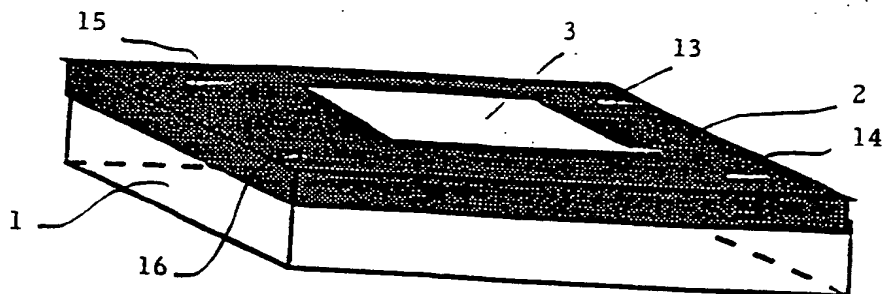


FIG. 1a

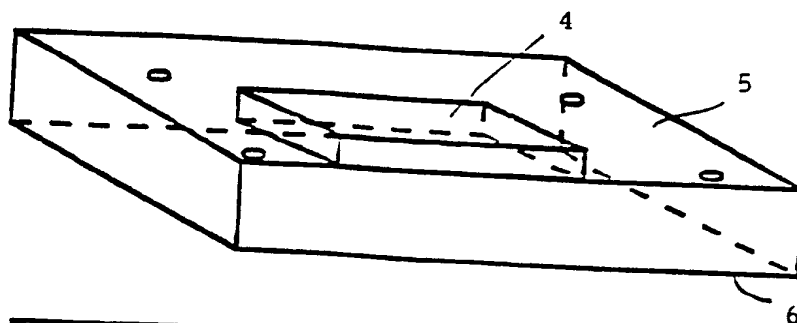


FIG. 1b

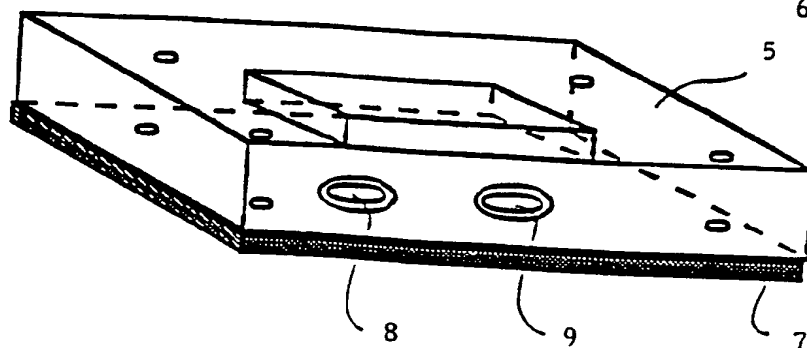


FIG. 1c

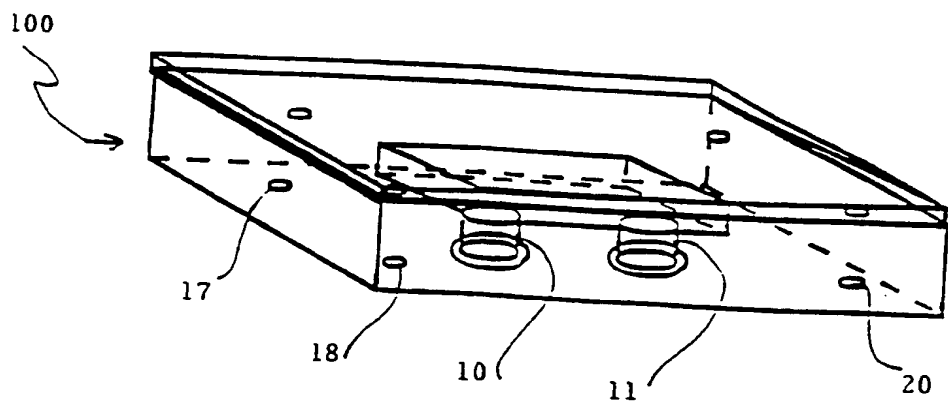
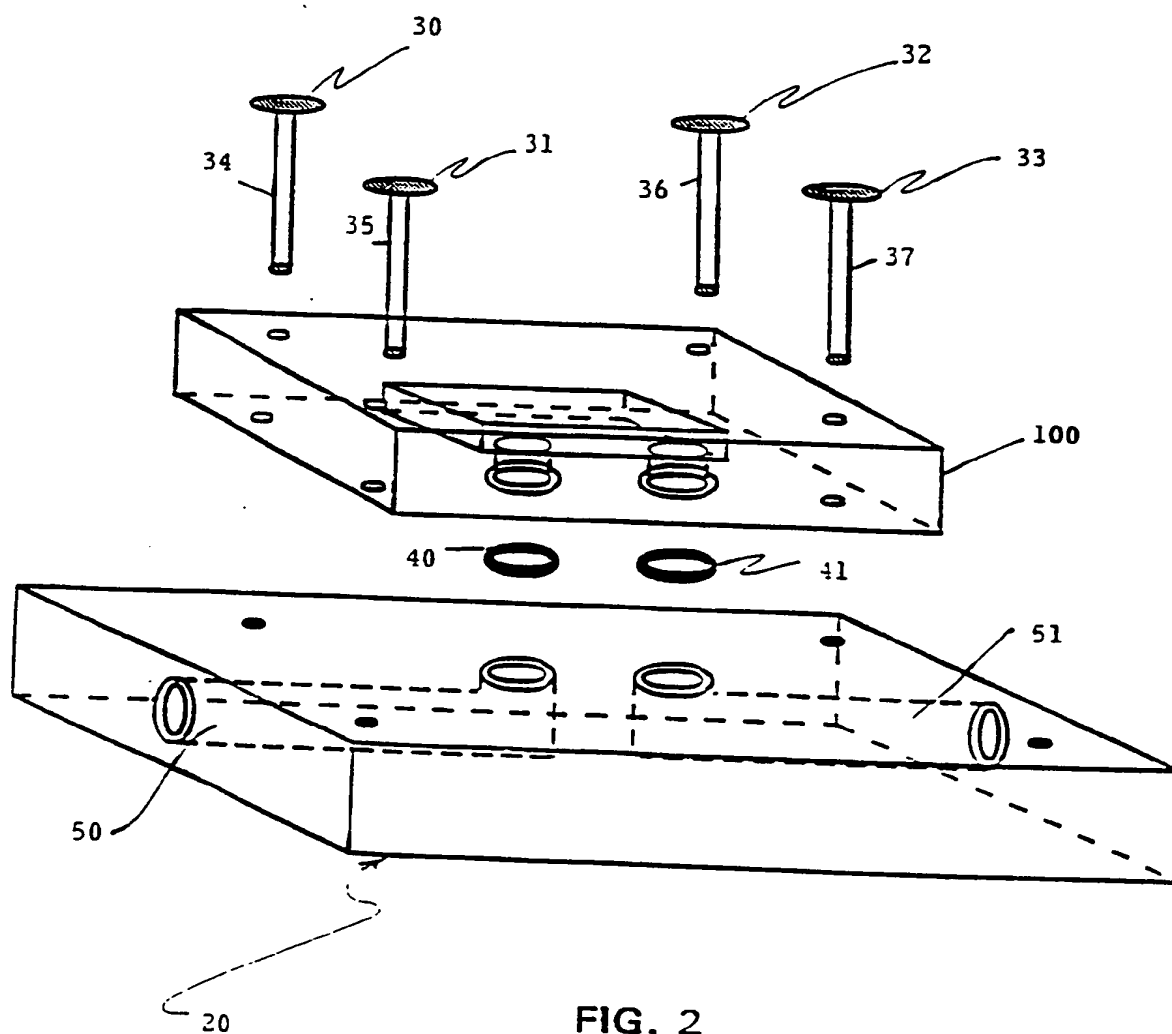


FIG. 1d



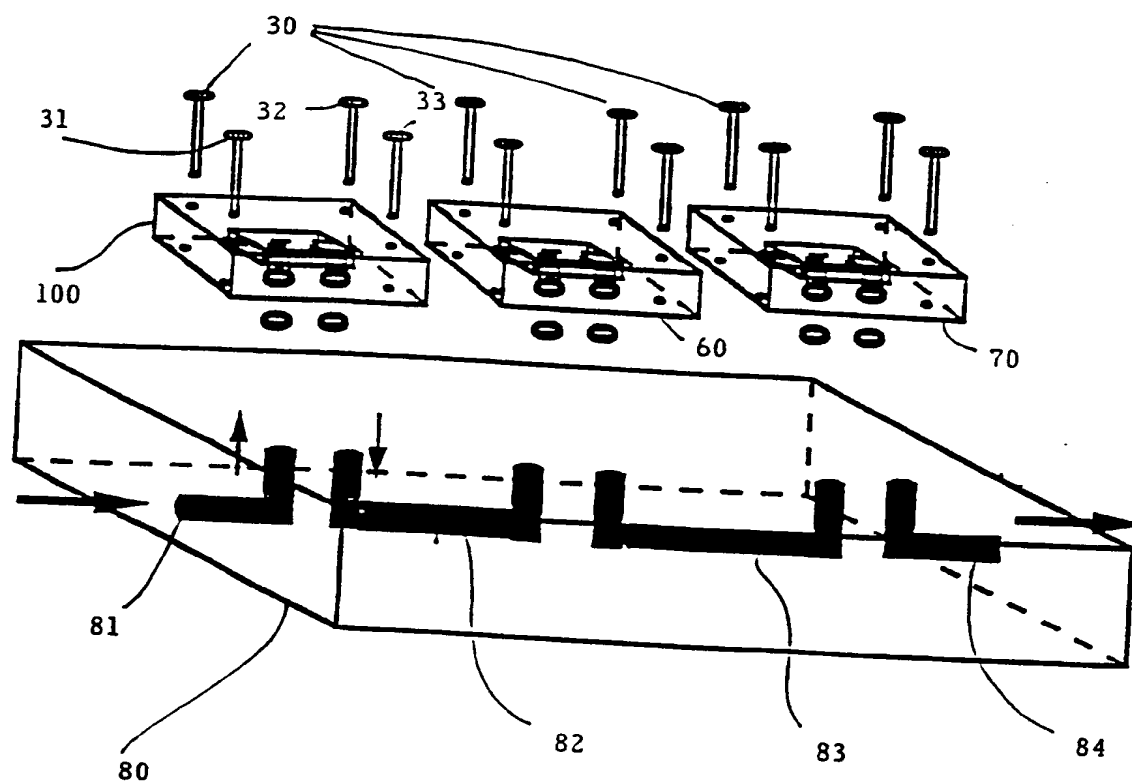


FIG. 3

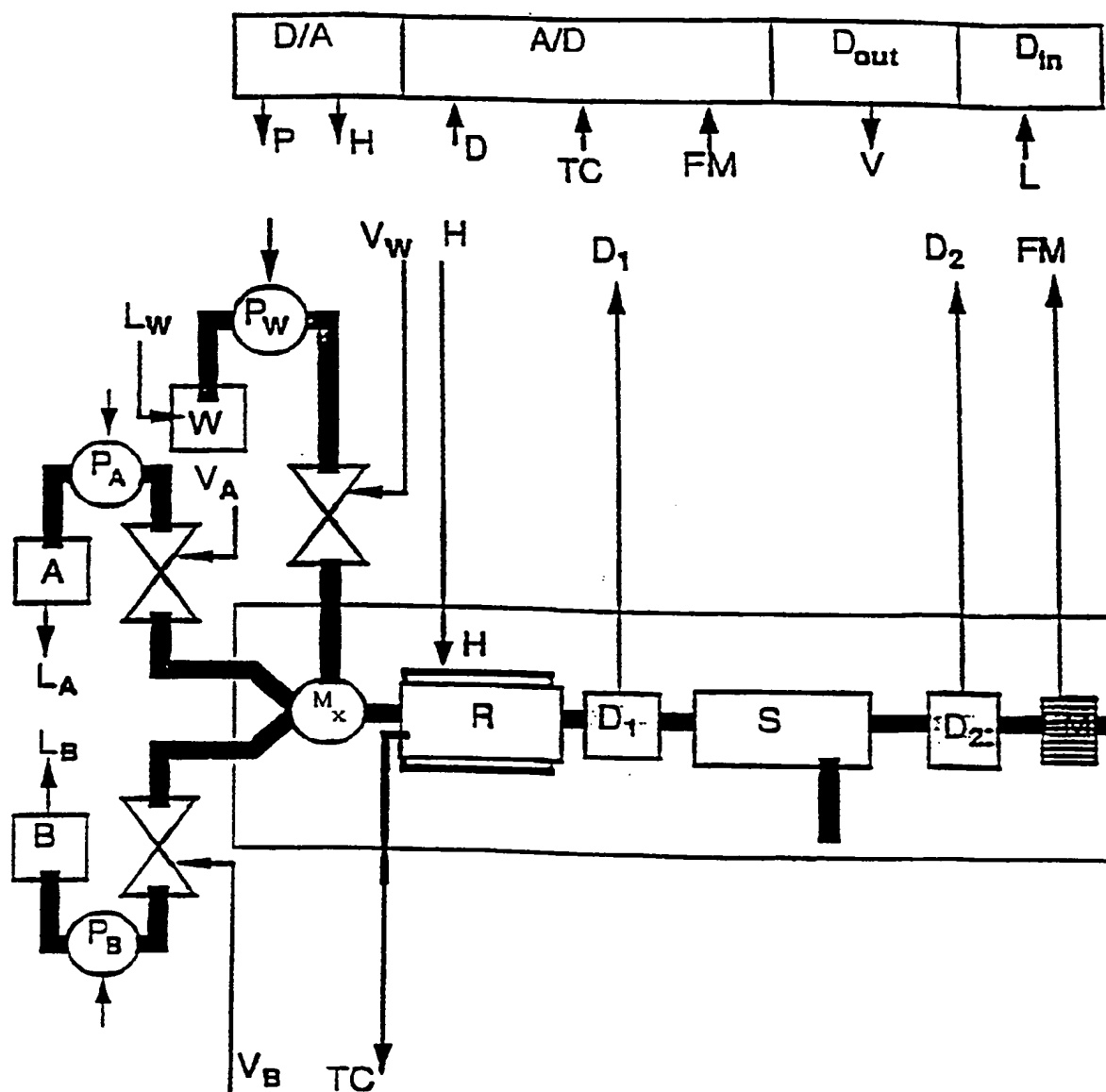


FIG. 4

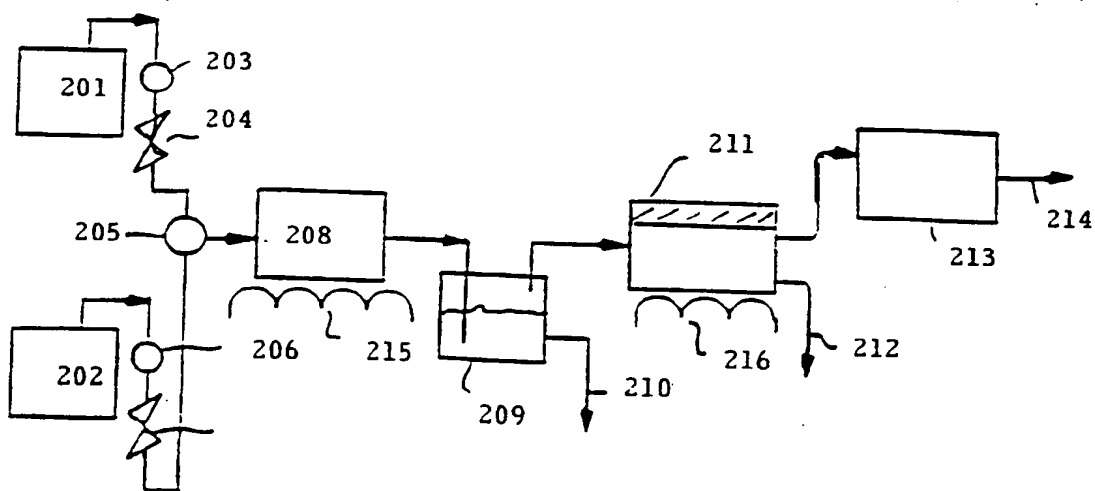


FIG. 5

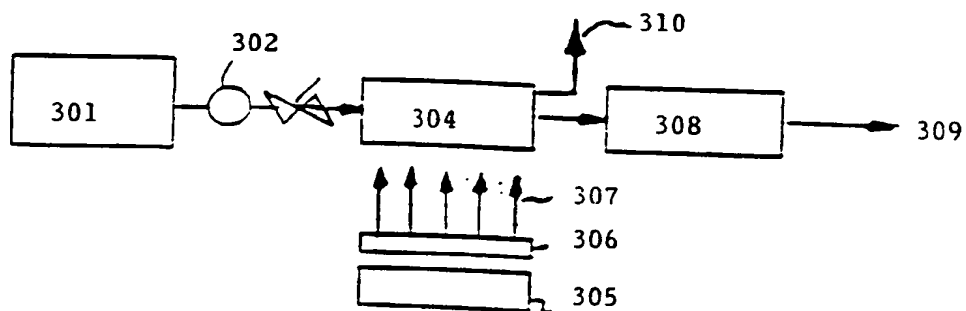


FIG. 6

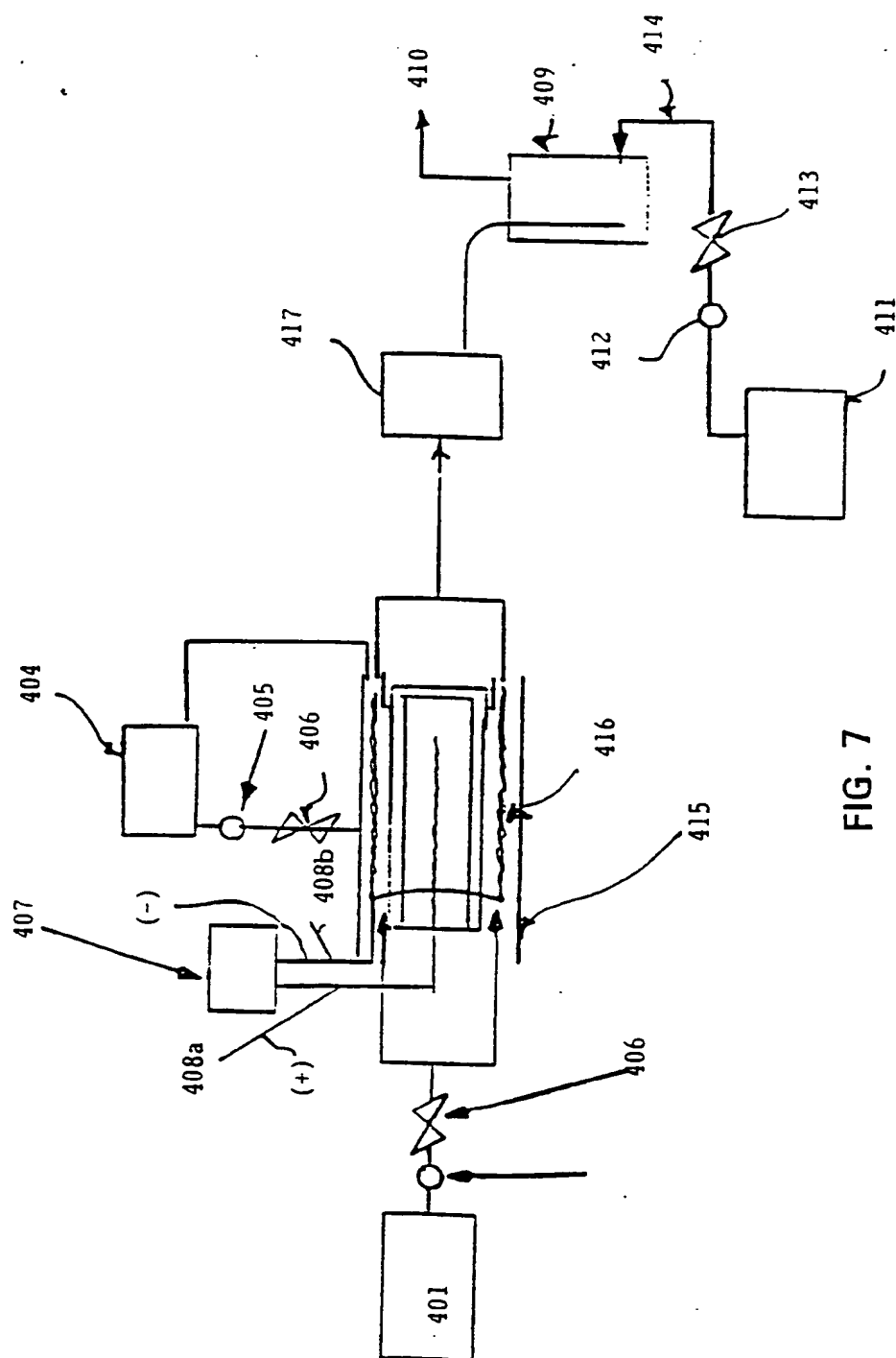


FIG. 7

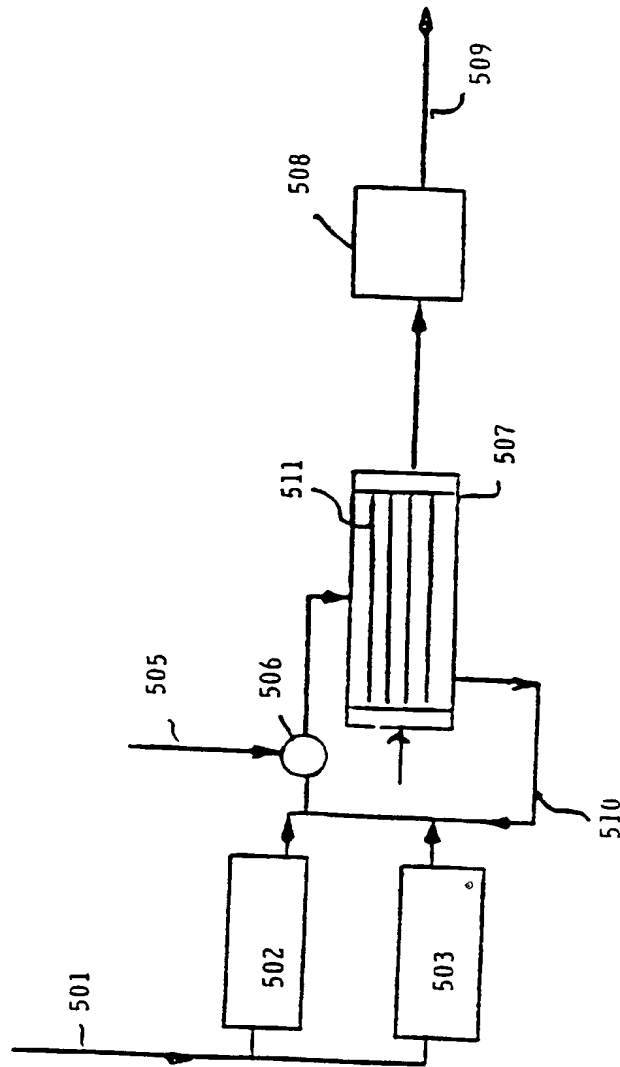


FIG. 8

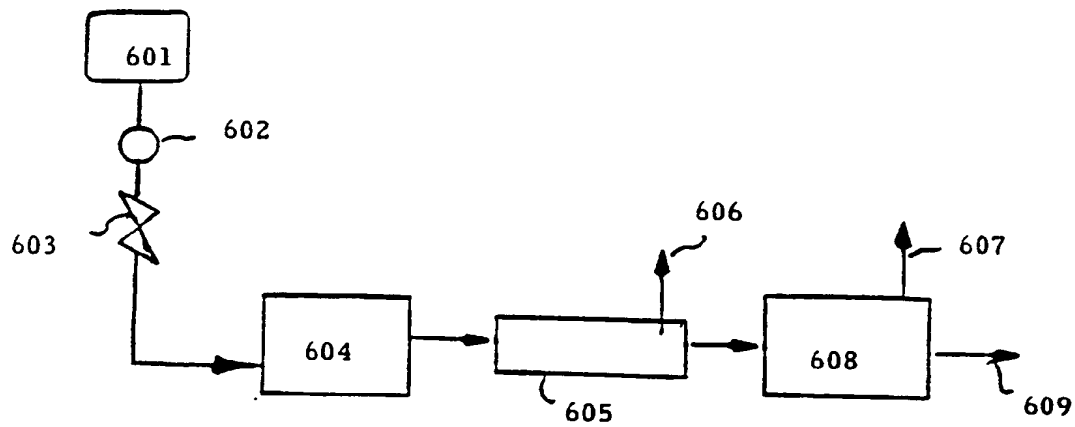


FIG. 9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/03873

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :B01D 15/08; G01N 33/00

US CL :422/81

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 422/52, 54, 63, 64, 68.1, 81, 102, 103

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 5,132,012 (MIURA ET AL.) 21 July 1992, see column 7.	10-13
Y	US, A, 5,250,263 (MANZ) 05 October 1993, see figures 11-13.	1-9,14-16
A	US, A, 5,252,294 (KROY ET AL.) 12 October 1993, see entire document.	1-16

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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P document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

23 JUNE 1995

Date of mailing of the international search report

12 JUL 1995

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